

Divergent C-H Insertion–Cyclization Cascades of N-Allyl Ynamides

Adcock, Holly V.; Chatzopoulou, Elli; Davies, Paul W.

DOI:

[10.1002/ange.201507167](https://doi.org/10.1002/ange.201507167)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Adcock, HV, Chatzopoulou, E & Davies, PW 2015, 'Divergent C-H Insertion–Cyclization Cascades of N-Allyl Ynamides', *Angewandte Chemie*, vol. 54, no. 51, pp. 15525-15529. <https://doi.org/10.1002/ange.201507167>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Eligibility for repository : checked 11/11/2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Divergent C–H Insertion–Cyclization Cascades of *N*-Allyl Ynamides

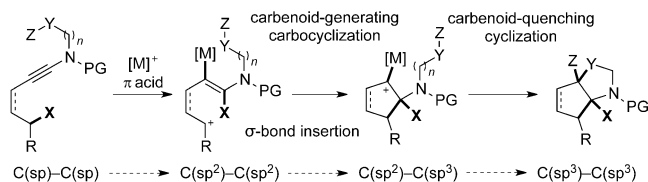
Holly V. Adcock, Elli Chatzopoulou, and Paul W. Davies*

Abstract: Gold carbene reactivity patterns were accessed by ynamide insertion into a $C(sp^3)$ –H bond. A substantial increase in molecular complexity occurred through the cascade polycyclization of *N*-allyl ynamides to form fused nitrogen-heterocycle scaffolds. Exquisite selectivity was observed despite several competing pathways in an efficient gold-catalyzed synthesis of densely functionalized $C(sp^3)$ -rich polycycles and a copper-catalyzed synthesis of fused pyridine derivatives. The respective gold–keteniminium and ketenimine activation pathways have been explored through a structure–reactivity study, and isotopic labeling identified turnover-limiting C–H bond cleavage in both processes.

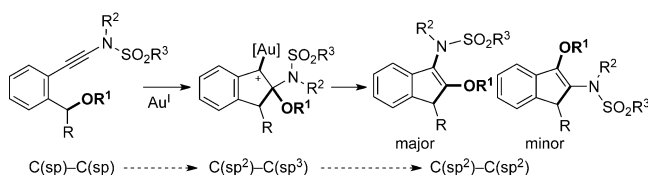
Access to molecules with stereogenic centers and a higher fraction of $C(sp^3)$ is increasingly desirable in pharmaceutical fragment design and lead discovery, as it is associated with improving chances of clinical success.^[1] The use of π -acid catalysis to generate metal–carbene character directly from triple bonds offers a rapid route to molecular complexity.^[2] Ynamides are attracting increasing attention in this regard, as the polarized π -system allows for regioselective carbenoid formation in the presence of other π -systems, oxidants, or nitrenoids.^[3–5] Potent transformations based on this approach enable the elaboration of a $C(sp)$ – $C(sp)$ unit into $C(sp^2)$ – $C(sp^2)$ or $C(sp^3)$ – $C(sp^2)$ units. We envisioned that the challenging $C(sp^3)$ – $C(sp^3)$ system might be directly accessed from ynamides if a carbenoid could be generated by σ -bond insertion and then quenched by cyclization onto the nitrogen substituent (Scheme 1 a).

With reference to this strategy, a gold carbene was formed previously by the formal insertion of an ynamide into a C–O σ -bond (Scheme 1 b).^[6,7] However, further cyclization was not observed. Instead, 1,2-migration dominated to give indenyl amides, regardless of the substituents present. Herein we show that carbenoid-based polycyclization can be induced by the $C(sp^3)$ –H insertion of ynamides (Scheme 1 c).^[8–10] Notably, exquisite selectivity was established over several divergent pathways in the preparation of heteroaromatic compounds or *N*-heterocycles with three new $C(sp^3)$ – $C(sp^3)$

a) Concept: Elaboration of ynamides with the introduction of new $C(sp^3)$ centers

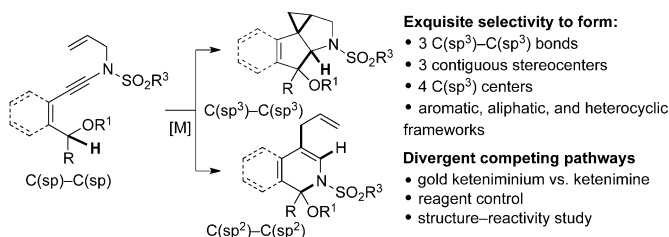


b) Formation and evolution of gold carbenes from ynamides by C–O σ -bond insertion^[6]



- R = aryl; R¹/R² = alkyl, aryl, benzyl, allyl; R³ = aryl, Me
- fast 1,2-N/O migration \rightarrow no polycyclization

c) Formation and evolution of gold carbene from ynamides by C–H σ -bond insertion



Scheme 1. Generation of gold carbenes from ynamides by carbocyclization. PG = protecting group.

bonds, three new fused rings, and up to four contiguous stereocenters.

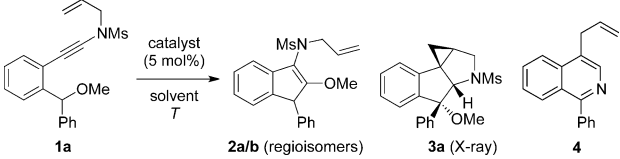
An ynamide polycyclization cascade was pursued by the use of an *N*-allyl substituent as a viable carbenoid-quenching unit.^[5h,i,n,11] Although several Au^I species/solvent combinations afforded only indenyl amides **2a/b** at room temperature, a breakthrough occurred when **1a** was heated with [Au(picolinate)Cl₂]^[12] in toluene (Table 1, entries 1 and 2; see also the Supporting Information). New diastereomeric products **3a** arose from insertion into the benzylic C–H σ -bond rather than the C–O σ -bond. The relative configuration across the fused ring junction is fixed. The methoxy group in **3a** is *anti* to the cyclopropyl methylene unit in the major diastereomer (see the Supporting Information).^[13] The product distribution depended on the temperature, solvent, and catalyst.^[14] Indenes **2a/b** were favored at lower temperatures and in more polar solvents (Table 1, entries 3–6; see also the Supporting Information). At higher temperatures, the use of AuCl₃ or AuBr₃ gave **3a** in lower yield and a 1,4-disubstituted isoquinoline **4** (Table 1, entries 7–10; see also the Supporting Information), which was also the main product with Au^I species. Degradation of **1a** was seen with BF₃·OEt₂, whereas

[*] Dr. H. V. Adcock, E. Chatzopoulou, Dr. P. W. Davies
School of Chemistry
University of Birmingham, Birmingham (UK)
E-mail: p.w.davies@bham.ac.uk

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/10.1002/anie.201507167>.

© 2015 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Table 1: Effect of reaction conditions on product distribution.^[a]



Entry	Catalyst	Solvent	T [°C]	Yield [%] ^[b] 1a/2a/2b/3a(d.r.)/4
1 ^[c]	[(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl]/AgNTf ₂	CH ₂ Cl ₂	RT	—:74:9:—:—
2	[Au(picolate)Cl ₂]	toluene	80	—:21:7:61(3.4:1):—
3	[Au(picolate)Cl ₂]	toluene	RT	—:54:32:9:—
4	[Au(picolate)Cl ₂]	MeNO ₂	80	—:45:19:9:—
5	[Au(picolate)Cl ₂]	toluene	100	—:11:6:66(2.9:1):—
6	[Au(picolate)Cl ₂]	<i>p</i> -xylene	120	—:7:5:75(2.3:1) ^[c] :—
7	AuBr ₃	<i>p</i> -xylene	120	—:8:4:48(2.4:1):<5
8	AuCl ₃	<i>p</i> -xylene	120	—:7:3:32(1.7:1):22
9	[Ph ₃ PAuCl]/AgNTf ₂	<i>p</i> -xylene	120 ^[d]	—:—:—:—:41
10	[(JohnPhos)Au(NCMe)]·SbF ₆	<i>p</i> -xylene	120 ^[d]	—:—:—:<5:27
11	BF ₃ ·OEt ₂	toluene	80	—:—:—:—:—
12	none	<i>p</i> -xylene	120 ^[e]	23:—:—:—:16
13	CuI	toluene	100 ^[f]	—:—:—:—:68 ^[g]

[a] General reaction conditions: **1a** (0.1 mmol, 1.0 equiv), catalyst (5 mol%), solvent (0.1 M); the reaction mixture was stirred for 6 h unless otherwise stated. [b] Yields were determined by ¹H NMR spectroscopy. The diastereomeric ratio of **3a** is given in parenthesis. [c] The major diastereomer is shown (isolated in 49% yield). [d] Reaction time: 3 h. [e] Reaction time: 24 h. [f] Reaction time: 8 h. [g] Product **4** was isolated in 65% yield. Ms = methanesulfonyl, JohnPhos = 2-(di-*tert*-butylphosphanyl)biphenyl, Tf = trifluoromethanesulfonyl.

4 was formed in low yield on heating without an added catalyst (Table 1, entries 11 and 12). The use of CuI in toluene at 100°C provided an effective balance between conversion into **4** and degradation (Table 1, entry 13; see also the Supporting Information).

Having established reagent control of the competing pathways for the cyclization of **1a**, we undertook a structure–reactivity investigation. Intriguingly, the *N*-*p*-toluenesulfonyl ynamide **1b** underwent faster and cleaner polycyclization to give **3b** in excellent yield with no carboalkoxylation, even at room temperature (Scheme 2). Preorganization of the substituents may prevent adoption of the reactive geometry for carboalkoxylation.^[6] Further studies with *N*-Ts ynamides showed that the C–H donor site could incorporate an allyloxy group (product **3c**) and an electron-deficient aryl substituent (product **3d**). The electron-rich aryl substituent in **1e** was not tolerated.^[15]

Polycycles bearing a protected ketone could be accessed as single diastereomers by incorporating a dioxolane unit in the alkyne starting material instead of the benzyldic moiety. Dimethylacetal and dioxane groups degraded under the reaction conditions; however, both **1f** and its *N*-nosylated analogue **1g** reacted smoothly, although **1g** required heating. Substituted dioxolanes were also reactive (products **3h,i**). The formation of **3i** as an unequal mixture of diastereomers from chiral-diol-derived **1i** provides promise for a future asymmetric synthesis of these complex *N*-heterocycles by a traceless-auxiliary approach. Interestingly, diastereoselectivity was also observed with an α -methyl-*N*-allyl group; thus, product **3j** was obtained with d.r. 4.0:1.

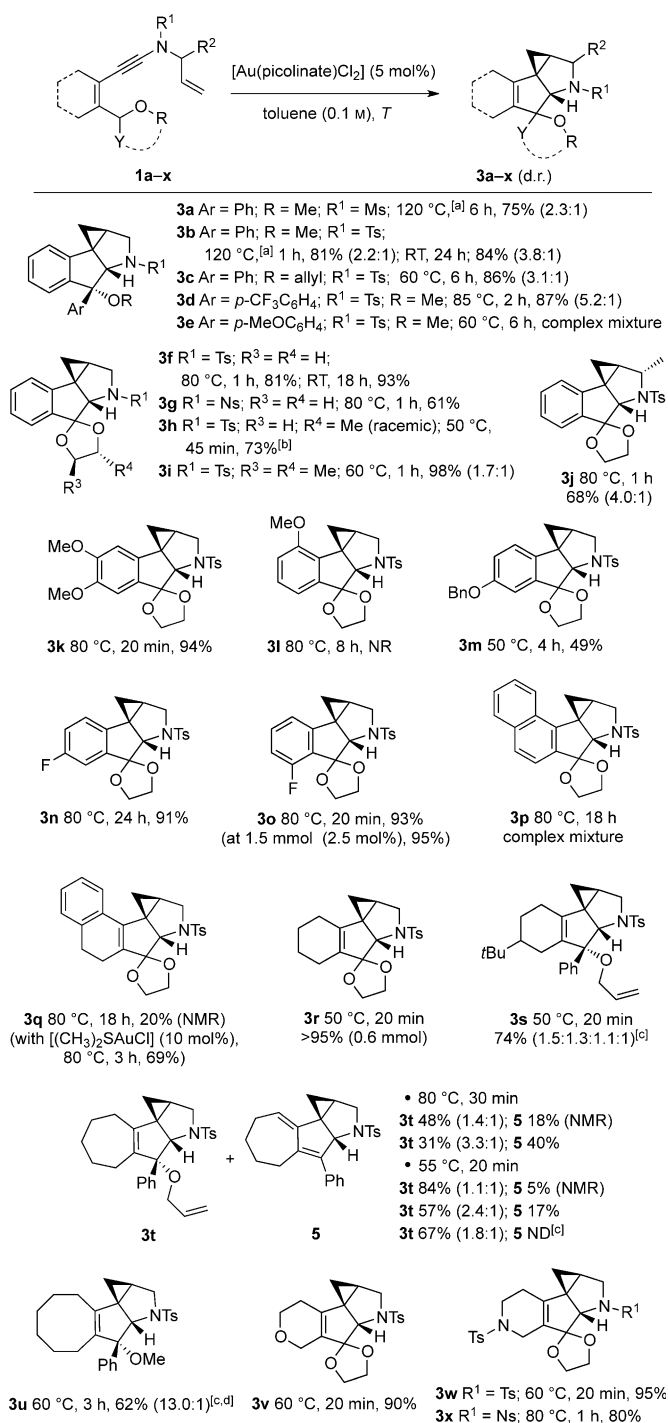
Electron-donating and electron-withdrawing groups were well tolerated (products **3k** and **3m–o**), and a larger-scale reaction of **1o** proceeded smoothly with a reduced catalyst loading. In contrast, substrates **1l,p** with large groups flanking the ynamide did not undergo the desired transformation. The less rigid dihydronaphthalene-substituted ynamide **1q** reacted only slowly with the Au^{III} catalyst to give **3q**, which was obtained in substantially improved yield with a linear Au^ICl equivalent. This result is consistent with gold atom needing to be in plane with the hydrocarbon skeleton linking to the hydride-donor site.

The non-aromatic C(sp³)-rich polycycles **3r–x** incorporating cycloalkyl, piperidine, and pyran motifs were assembled readily. The gold-catalyzed reactions proceeded smoothly, though products **3s–u** from benzylic ethers required careful handling and purification on deactivated silica. As illustrated with **3t**, although the catalysis is

sufficiently mild to afford the product in high yield after 20 min at 55°C, the polycyclization product undergoes elimination (to diene **5** in the case of **3t**) on further heating or on exposure to silica (yields and diastereomeric ratios determined by NMR spectroscopy and after purification by column chromatography on silica gel are shown in Scheme 2 for two different reaction temperatures).

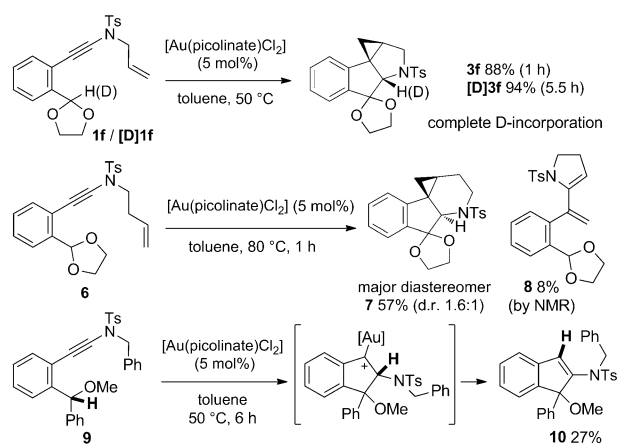
Further mechanistic insight into the polycyclization was then sought. Complete deuterium transfer from the benzylic site to the bridgehead position adjacent to the nitrogen atom was observed with [D]**1f** (Scheme 3). The quantitative analysis of initial reaction rates was hampered by an induction period (see the Supporting Information for an NMR study);^[12] however, an approximately fivefold increase in reaction time was required over that for **1f**.^[16,17] *N*-Homoallyl ynamide **6** was converted into the piperidine-fused polycycle **7** as the major product. Only a small amount of amidodiene **8** from ene–ynamide cycloisomerization was observed, thus showing C–H insertion to be kinetically more productive than the attack of an alkene.^[5a,b] *N*-Benzyl ynamide **9** did not undergo polycyclization, but instead C–H insertion occurred to afford indenyl amide **10**.^[18] Although further investigation is needed to explore the full scope of the polycyclization, the successful reaction with the more rotationally labile homoallyl group is promising.

Isoquinoline formation from *N*-methanesulfonyl ynamides **1a/y** could be interrupted by adding a base to afford alkoxy 1,2-dihydroisoquinolines **11a,y**, which were readily converted into **4** (Scheme 4). The conversion of [D]**1a** took approximately twice as long as that of **1a** and led to full

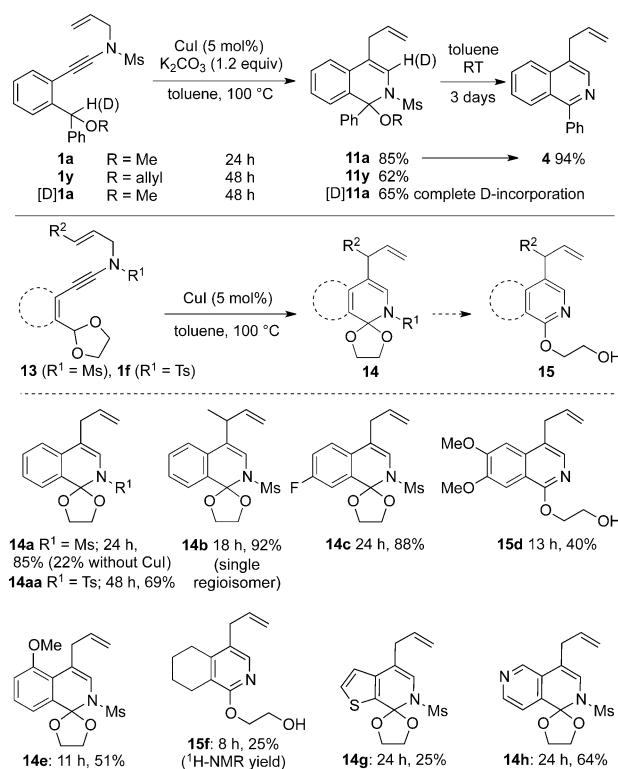


Scheme 2. Structural effects on the ynamide C–H insertion–cyclopropanation cascade. Yields are for the isolated product after flash column chromatography. In each case, the major diastereomer is shown. [a] *o*-Xylene (0.1 M) was used as the solvent. [b] Product **3h** was isolated as a complex mixture of four diastereomers. [c] The product was purified on NEt₃-deactivated silica. [d] The diastereomeric ratio before purification was 3.1:1. NR=no reaction, Ns=4-nitrobenzenesulfonyl, Ts=*p*-toluenesulfonyl.

deuterium incorporation at the 3-position. The products derived from dioxolane derivatives **13a–h** were generally isolated as dialkoxy 1,2-dihydroisoquinolines **14** unless elimination was aided by the substitution pattern (product **15d**) or



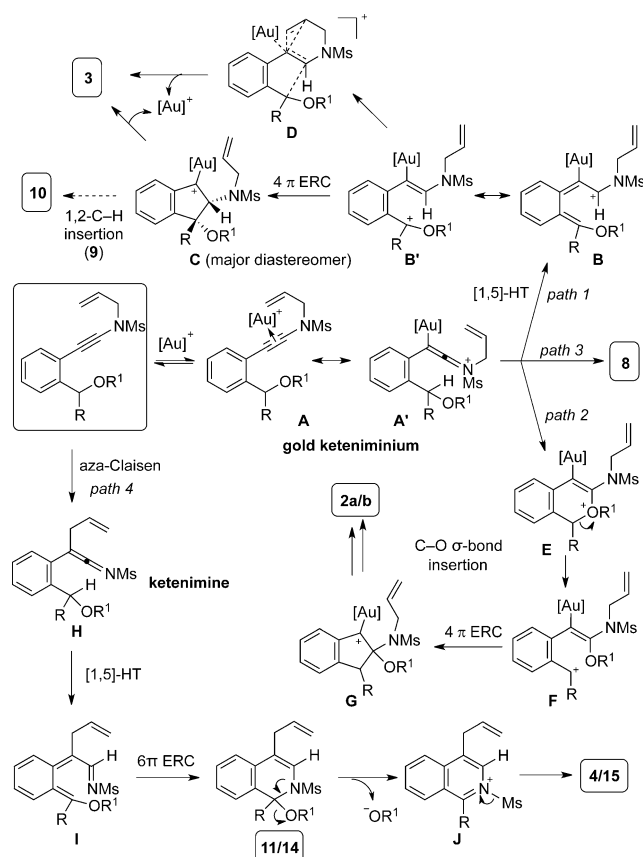
Scheme 3. Reactions to probe individual steps within the polycyclization cascade.



Scheme 4. Initial exploration of the ynamide cascade cyclization initiated by an aza-Claisen reaction.

aromatization (product **15f**). In stark contrast to the polycyclization, *N*-Ms ynamides gave faster and cleaner reactions than *N*-Ts ynamides (**14a** vs. **14aa**; **4** was formed in 20% yield from **1b**). The rearrangement cascade also tolerated increased substitution around the ynamide (product **14e**) and electronic variation (products **14c–e**). The reactions of thiophene- and pyridine-derived ynamides highlight the ability to access other desirable heteroaromatic motifs (products **14g,h**).^[19]

According to our observations and previously reported studies, the reactions can be rationalized on the basis of competing activation of the substrate as a gold keteniminium



Scheme 5. Proposed mechanistic outline of competing pathways. For clarity, conformational changes are not shown. ERC = electrocyclic ring closure.

intermediate **A/A'** and ketenimine **H** (Scheme 5). Deuterium labeling and the impact of (de)stabilizing substituents (see products **3k,n,o**^[20] in Scheme 2) are consistent with the turnover-limiting formation of benzylic cation **B** by 1,5-hydride transfer from **A'** (path 1).^[21] The gold atom must be able to align in a plane with the carbon atom of the donor site (compare **11–q**). Stepwise cyclization, to give gold carbene **C**, and cyclopropanation would give **3**. An inverted order of bond formation, with cyclopropanation occurring before C–H insertion of a gold carbene,^[22] is unlikely on the basis of the results with **6** and **9**. The general lack of competition from 1,2-C–H insertion of **C** at adjacent heteroatom-substituted positions (compare the formation of **10** from **9**) is surprising^[2,23] and could result from a more concerted polycyclization event (see **D**), which would also account for the diastereoselection at the ring junction in the presence of a chiral N-substituent (formation of **3j**). This interaction is not, however, required for metal carbene formation by C–H insertion, as seen with **10**, in which case 1,2-insertion followed cyclization.

Attack of the ether oxygen atom or homoallyl group can lead to competing carbocyclizations of intermediate **A** (paths 2 and 3). Although carboalkoxylation is favored at lower temperatures, a thermal aza-Claisen pathway^[24] can compete at higher temperatures and outperform π -activation pathways in the absence of a sufficiently electrophilic catalyst (path 4). A 1,5-hydride shift onto ketenimine **H** occurs in

place of the 1,3-sulfonyl shift shown to be facile with aryl ynesulfonamides.^[24] A 6π electrocyclic ring closure would give the isolable heterocycles **11/14**.^[25,26] Neighboring-group-assisted elimination and desulfonylation would then afford **4/15**. A metal catalyst could potentially play a role during each stage of this thermally viable cascade.

In summary, the induction of gold carbene character by ynamide insertion into a C(sp³)–H bond resulted in a novel polycyclization cascade of *N*-(homo)allyl ynamides. Superb selectivity was observed for an array of competing processes through the appropriate choice of reaction conditions and was reinforced by structural effects. Two protocols were developed to access substantial molecular complexity in a single step with simple catalysts and practically straightforward reaction conditions: Fused C(sp³)-rich scaffolds resulted from a gold keteniminium pathway, in which C–H insertion outperformed carboalkoxylation and enyne cycloisomerization, and heteroaromatic pyridine-fused derivatives were prepared through ketenimine activation in a copper-catalyzed rearrangement cascade. Investigations are ongoing to further elucidate the mechanism, stereocontrol factors, and wider synthetic potential of these reactions.

Acknowledgements

We thank the EPSRC and AstraZeneca plc (Studentship to H.V.A.) and the University of Birmingham (Studentship to E.C.) for funding, Dr. Louise Male (University of Birmingham) for X-ray crystallography, and Dr. Thomas Langer (AstraZeneca plc, Macclesfield, UK) for interesting discussions. Facilities used in this research were in part supported through Birmingham Science City AM2 by AWM and the ERDF.

Keywords: carbenes · cyclopropanation · gold · nitrogen heterocycles · ynamides

- [1] a) F. Lovering, *Med. Chem. Commun.* **2013**, 4, 515; b) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, 52, 6752.
- [2] For selected reviews, see: a) D. J. Gorin, F. D. Toste, *Nature* **2007**, 446, 395; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, 46, 3410; *Angew. Chem.* **2007**, 119, 3478; c) A. S. K. Hashmi, *Chem. Rev.* **2007**, 107, 3180; d) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, 115, 9028; e) P. W. Davies, M. Garzón, *Asian J. Org. Chem.* **2015**, 4, 694.
- [3] For reviews on ynamides, see: a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, 110, 5064; b) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, 49, 2840; *Angew. Chem.* **2010**, 122, 2902; c) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, 47, 560.
- [4] For the synthesis of ynamides, see: a) Y. S. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, 6, 1151; b) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, 130, 833; c) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* **2009**, 48, 4381; *Angew. Chem.* **2009**, 121, 4445;





- d) S. J. Mansfield, C. D. Campbell, M. W. Jones, E. A. Anderson, *Chem. Commun.* **2015**, 51, 3316.
- [5] For examples of reactions with π -systems, see: a) S. Couty, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2006**, 45, 6726; *Angew. Chem.* **2006**, 118, 6878; b) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, 6, 1509; c) A. S. K. Hashmi, M. Rudolph, J. W. Bats, W. Frey, F. Rominger, T. Oeser, *Chem. Eur. J.* **2008**, 14, 6672; d) S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2011**, 50, 5090; *Angew. Chem.* **2011**, 123, 5196; for examples of reactions with oxidants, see: e) P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2011**, 47, 379; f) C.-W. Li, K. Pati, G.-Y. Lin, S. A. Sohel, H.-H. Hung, R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, 49, 9891; *Angew. Chem.* **2010**, 122, 10087; g) D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das, R.-S. Liu, *Angew. Chem. Int. Ed.* **2011**, 50, 6911; *Angew. Chem.* **2011**, 123, 7043; h) K.-B. Wang, R.-Q. Ran, S.-D. Xiu, C.-Y. Li, *Org. Lett.* **2013**, 15, 2374; i) R. Liu, G. N. Winston-McPherson, Z.-Y. Yang, X. Zhou, W. Song, I. A. Guzei, X. Xu, W. Tang, *J. Am. Chem. Soc.* **2013**, 135, 8201; j) M. D. Santos, P. W. Davies, *Chem. Commun.* **2014**, 50, 6001; k) L. Li, C. Shu, B. Zhou, Y.-F. Yu, X.-Y. Xiao, L.-W. Ye, *Chem. Sci.* **2014**, 5, 4057; for examples of reactions with nitrenoids, see: l) C. Li, L. Zhang, *Org. Lett.* **2011**, 13, 1738; m) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed.* **2011**, 50, 8931; *Angew. Chem.* **2011**, 123, 9093; n) Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2014**, 16, 3138; o) M. Garzón, P. W. Davies, *Org. Lett.* **2014**, 16, 4850; p) A.-H. Zhou, Q. He, C. Shu, Y.-F. Yu, S. Liu, T. Zhao, W. Zhang, X. Lu, L.-W. Ye, *Chem. Sci.* **2015**, 6, 1265; q) L. Zhu, Y. Yu, Z. Mao, X. Huang, *Org. Lett.* **2015**, 17, 30.
- [6] H. V. Adcock, T. Langer, P. W. Davies, *Chem. Eur. J.* **2014**, 20, 7262.
- [7] For a review on insertion into C–X σ -bonds, see: H. V. Adcock, P. W. Davies, *Synthesis* **2012**, 44, 3401.
- [8] For impressive super-acid-mediated cationic cascades of aromatic ynamides with insertion at unfunctionalized benzylic positions, see: C. Theunissen, B. Métayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudau, G. Evano, *J. Am. Chem. Soc.* **2014**, 136, 12528.
- [9] For reviews on C–H insertion, see: a) L. Wang, J. Xiao, *Adv. Synth. Catal.* **2014**, 356, 1137; b) M. C. Haibach, D. Seidel, *Angew. Chem. Int. Ed.* **2014**, 53, 5010; *Angew. Chem.* **2014**, 126, 5110; J. Xie, C. Pan, A. Abdukader, C. Zhu, *Chem. Soc. Rev.* **2014**, 43, 5245.
- [10] For the formation of C(sp²)–C(sp³) bonds from alkynes under Au catalysis, see: a) I. D. Jurberg, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, 132, 3543; b) J. Barluenga, R. Sigüeiro, R. Vicente, A. Ballesteros, M. Tomás, M. A. Rodríguez, *Angew. Chem. Int. Ed.* **2012**, 51, 10377; *Angew. Chem.* **2012**, 124, 10523; c) M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, 52, 2593; *Angew. Chem.* **2013**, 125, 2653; d) L. Ye, Y. Wang, D. H. Aue, L. Zhang, *J. Am. Chem. Soc.* **2012**, 134, 31; e) G. Cera, M. Chiarucci, F. Dosi, M. Bandini, *Adv. Synth. Catal.* **2013**, 355, 2227; for their formation under Pt catalysis, see: f) P. A. Vadola, D. Sames, *J. Am. Chem. Soc.* **2009**, 131, 16525; for the formation of C(sp²)–C(sp³) bonds from alkynes under Au catalysis, see: g) G. Lemièrre, V. Gandon, N. Agenet, J.-P. Goddard, A. de Kozak, C. Aubert, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2006**, 45, 7596; *Angew. Chem.* **2006**, 118, 7758; for their formation under Pt catalysis, see: h) D. Vasu, A. Das, R.-S. Liu, *Chem. Commun.* **2010**, 46, 4115.
- [11] For a review, see: a) D. Qian, J. Zhang, *Chem. Soc. Rev.* **2015**, 44, 677.
- [12] A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejović, *Angew. Chem. Int. Ed.* **2004**, 43, 6545; *Angew. Chem.* **2004**, 116, 6707.
- [13] CCDC 1410362 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [14] For recent examples of gold-catalyst-controlled pathway divergence, see: a) C.-D. Wang, Y.-F. Hsieh, R.-S. Liu, *Adv. Synth. Catal.* **2014**, 356, 144; b) L.-Y. Mei, Y. Mei, X.-Y. Tang, M. Shi, *J. Am. Chem. Soc.* **2015**, 137, 8131; c) N. Morita, A. Yasuda, M. Shibata, S. Ban, Y. Hashimoto, I. Okamoto, O. Tamura, *Org. Lett.* **2015**, 17, 2668; d) W. Rao, D. Susanti, B. J. Ayers, P. W. H. Chan, *J. Am. Chem. Soc.* **2015**, 137, 6350; e) G. Xu, C. Zhu, W. Gu, J. Li, J. Sun, *Angew. Chem. Int. Ed.* **2015**, 54, 883; *Angew. Chem.* **2015**, 127, 897; for a general review, see: f) J. Mahatthanachai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, 51, 10954; *Angew. Chem.* **2012**, 124, 11114.
- [15] This result could potentially be due to an aryl–ynamide interaction; see: C. Wang, X. Xie, J. Liu, Y. Liu, Y. Li, *Chem. Eur. J.* **2015**, 21, 559.
- [16] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, 51, 3066; *Angew. Chem.* **2012**, 124, 3120.
- [17] At a 0.27 M concentration, **1f** was consumed in 70 min; 72 % of [**D**]**1f** was consumed in 6 h.
- [18] For indene formation by alkyne insertion into benzylic C–H bonds under Pt/Ru catalysis, see: a) M. Tobisu, H. Nakai, N. Chatani, *J. Org. Chem.* **2009**, 74, 5471; b) S. Yang, Z. Li, X. Jian, C. He, *Angew. Chem. Int. Ed.* **2009**, 48, 3999; *Angew. Chem.* **2009**, 121, 4059; c) G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, 71, 6204; for Au catalysis, see: d) P. Morán-Poladura, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2015**, 54, 3052; *Angew. Chem.* **2015**, 127, 3095.
- [19] Neither substrate proved reactive in the polycyclization. This result is consistent with a larger angle between the reaction centers in **A/A'** (Scheme 5) for a thiophene scaffold, and destabilization of the putative cation **B** by the pyridinyl group.
- [20] For an accelerating effect of substitution adjacent to the hydride-donor site, see: K. Mori, T. Kawasaki, S. Sueoka, T. Akiyama, *Org. Lett.* **2010**, 12, 1732.
- [21] The congested intermediates **B/B'** are drawn as if they were planar, but would be formed in atropisomeric conformations owing to the stereoelectronic requirements of a sigmatropic or through-space hydride shift. For a study on the role of rotational barriers in reaction pathways, see: O. N. Faza, C. S. López, A. R. de Lera, *J. Org. Chem.* **2011**, 76, 3791.
- [22] Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, 131, 2809; S. Bhunia, S. Ghorpade, D. B. Huplé, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, 51, 2939; *Angew. Chem.* **2012**, 124, 2993.
- [23] For a review, see: R. Dorel, A. M. Echavarren, *J. Org. Chem.* **2015**, 80, 7321.
- [24] For *N*-allyl ynesulfonamide aza-Claisen reactions, see: a) K. A. DeKorver, T. D. North, R. P. Hsung, *Synlett* **2010**, 16, 2397; b) K. A. Dekorver, R. P. Hsung, A. G. Lohse, Y. Zhang, *Org. Lett.* **2010**, 12, 1840; c) K. A. DeKorver, W. L. Johnson, Y. Zhang, R. P. Hsung, H. Dai, J. Deng, A. G. Lohse, Y.-S. Zhang, *J. Org. Chem.* **2011**, 76, 5092; d) K. A. Dekorver, R. P. Hsung, A. W.-Z. Song, X.-N. Wang, M. C. Walton, *Org. Lett.* **2012**, 14, 3214; e) X.-N. Wang, G. N. Winston-McPherson, M. C. Walton, Y. Zhang, R. P. Hsung, K. A. Dekorver, *J. Org. Chem.* **2013**, 78, 6233; f) Y. Zhang, K. A. Dekorver, A. G. Lohse, Y.-S. Zhang, J. Huang, R. P. Hsung, *Org. Lett.* **2009**, 11, 899; the allylic inversion in **14b** is consistent with the results of these studies.
- [25] L. Sun, Y. Zhu, P. Lu, Y. Wang, *Org. Lett.* **2013**, 15, 5894.
- [26] X.-Z. Shu, K.-G. Ji, S.-C. Zhao, Z.-J. Zheng, J. Chen, L. Lu, X.-Y. Lui, Y.-M. Liang, *Chem. Eur. J.* **2008**, 14, 10556.

Received: August 1, 2015

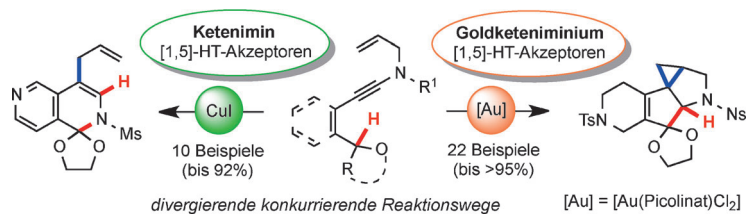
Revised: September 18, 2015

Published online: ■ ■ ■ ■ ■ ■ ■ ■ ■ ■



H. V. Adcock, E. Chatzopoulou,
P. W. Davies*    

Divergent C–H Insertion–Cyclization
Cascades of *N*-Allyl Ynamides



Konkurrenz belebt die Synthese: Divergente Cycloisomerisierungen von *N*-Allyl-ynamiden mit einfachen Katalysatoren bieten Zugang zu komplexen und dicht funktionalisierten Polycyclen. Struktur-Reaktivitäts-Studien offenbaren kon-

kurrierende C–H-Insertionsprozesse im Zuge der Aktivierung der Inamide in Form von Goldketeniminium- oder Ketenimin-Zwischenstufen (siehe Schema; HT = Wasserstofftransfer).